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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,974	06/20/2001	Mark Laurence Brader	X-11869	9992
25885	7590	10/11/2006	EXAMINER	
ELI LILLY & COMPANY PATENT DIVISION P.O. BOX 6288 INDIANAPOLIS, IN 46206-6288			ROBINSON, HOPE A	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/868,974	Applicant(s) BRADER ET AL.	
	Examiner Hope A. Robinson	Art Unit 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 July 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 34, 36, 37, 40, 41, 43, 44 and 47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 34, 36-37, 40-41, 43 and 47 is/are rejected.
- 7) ☒ Claim(s) 44 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed February 17, 2006 on July 25, 2006 is acknowledged.

Claim Disposition

2. Claims 34, 36-37, 40-41, 43-44 and 47 are pending and are under examination.

New-Claim Objection

3. Claim 44 is objected to because of the following informalities:

Claim 44 is objected because the claim depends from a rejected base claim.

Correction is required.

Withdrawn-Claim Rejection-35 USC 112

4. Previous rejection to the claims under 35 U.S.C. 112, second paragraph is withdrawn by virtue of applicant's arguments that the structure of the GLP-1 is universal, thus the same.

Maintained-Rejection - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

Art Unit: 1656

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 34, 36-37 and 40 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a shelf stable solution formulation comprising GLP-1, a preservative and tonicity modifier and a pH of 8.2-8.8. The specification on page 6 disclose that the present inventions provides a shelf stable formulation of GLP-1, GLP-1 analogs and GLP-1 derivatives; and the amide forms thereof. A skilled artisan cannot envision the detailed chemical structure of all the derivatives encompassed in the claims. The claims are directed to a large variable genus of GLP-1 associated molecules. The specification fails to provide any additional representative species of the claimed genus, to show that applicant was in possession of the claimed genus.

A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and

Art Unit: 1656

structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993).

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

6. Claims 34, 36-37 and 40 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the a shelf stable solution formulation comprising SEQ ID NO: 2 and GLP-1 analogs known in the art, does not reasonably provide enablement for any GLP-1 derivative or variant or amide form thereof. The specification does not enable any

Art Unit: 1656

person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)). The factors most relevant to the instant invention are discussed below.

Undue experimentation would be required to construct all the possible derivatives/variants encompassed in the claimed invention and test the same for a shelf-stable solution formulation to be administered to a patient suffering from diabetes. The art recognizes GLP-1 analogs, however, the changes contemplated in the claimed invention surpasses such a disclosure. Claim 34 for example provides a laundry list of changes that can be made, however, none is exemplified. SEQ ID NO:2 can have specific substitutions at a R1, X, Y, Z or R2 position (see for example claim 41), however, claim 34 recites "at least one modification" in association with a laundry list of possibilities, devoid of a showing of said derivative and its applicability. The art recognizes that GLP-1 analogs play a role in the treatment of diabetes, however, there is no showing of all the derivatives encompassed in the claims (see for example claim 40). No direct correlation is made between structure and function. In addition, there are no indicia as to what residue substitution

Art Unit: 1656

can be tolerated to retain stability and if the position of the residue will affect the formulation adversely. The specification on pages 9-10 provides a discussion of GLP-1 analogs and derivatives, however, the substitutions contemplated is limited to specific residues at specific positions in the sequence. Therefore, a skilled artisan would have to engage in undue experimentation to be able to determine if all possible substitutions result in a shelf stable formulation and if there are positions within the molecule that cannot tolerate the modifications contemplated, to practice the claimed invention commensurate in scope with the claims.

It is in no way predictable what changes can be tolerated in a protein's structure. Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of

Art Unit: 1656

binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The specification lacks guidance with regard to whether, for example, a substitution of an alanine at position 3 would be detrimental to the formulation, and in term the claimed method of treatment. In view of the foregoing, the specification lacks adequate guidance/direction to be enabling.

The working examples provided do not demonstrate or describe the claimed invention to enable the full scope of the claims.

The nature of the invention relates to a stable formulation in solution comprising GLP-1 with substitutions of specific residues at a specified position. The claimed product can also have a substitution of at least one additional amino acid in the protein structure. The prior art teaches GLP-1 analogs, with substitutions that retain stability, however, no support was found for all the substitutions claimed having no adverse effect on the formulation. For example, GLP-1 analogs (a molecule having one or more amino acid substitution) are disclosed in WO 91/11457 and they

Art Unit: 1656

include modification such as a substitution of glycine at position 26 or 34, and lists a number of substitutions that can also occur at positions 36, 31, 21, 22, 15 etc. Specific positions having specific residue substitutions are provided. The claimed formulation reads on at least one of the prescribed residue and any others from the laundry list of amino acids and any amounts since "at least one" includes, 10, 20, etc. There is no indication in the instant specification as to whether position 26 will have a "valine-isoleucine-leucine or valine- valine-valine, for example. These tripeptides are encompassed in the "at least one" recitation as well as more than three residues with a variety of arrangements.

The prior art generally acknowledges that a structural change in a protein's sequence can affect the function of the protein. Tuddenham et al. (Nucleic Acids Research, vol. 22, no. 17, pages 3511-3533, 1994) teach that substitution of an amino acid as alanine, as a result of the changes to the nucleotide sequence, have a significant functional impact on the polypeptide. Therefore, the substitutions contemplated within SEQ ID NO:2 can result in an unstable product, rendering the invention as unpredictable.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of derivatives of GLP-1. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired

Art Unit: 1656

biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims to be considered enabling.

Maintained-Claim Rejections - 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 34, 36, 40-41, 43 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated

by Hoffman (U.S. Patent No. 6,358,924, June 1, 2000).

Hoffman teaches a stable solution formulation comprising GLP-1 peptides, derivatives and GLP-1 analogs, for example GLP-1 (7-34) or the amide forms thereof, a pharmaceutically acceptable preservative (m-cresol) and a tonicity-modifying agent (glycerin) (claim 34, see columns 2, 4 and 5 of the patent). Hoffmann also teach a pH range of 6.5-9.0 which falls within the recited range. The formulation taught by Hoffmann contains at least one substitution selected from the group consisting of a glycine, serine, cysteine etc., at position 26 (see column 5), said 'at least one substitution' is identical to the instant application structure (i.e. SEQ ID NO:2 and the formulation in the instant claims 34 and 43). Hoffmann discloses that in the formulation arginine is replaced with lysine at position 34 (claim 36, see column 5, item a). Additionally, Hoffmann has a method of treating a person having diabetes or other conditions in which the administration of a GLP-1-like molecule is indicated (column 2, claims 40 and 47 of the instant specification). Further, the formulation recited in the instant claim 41 is anticipated as Hoffmann discloses the same formulation (see the bottom of column 4 of the patent). Therefore, the limitations of the claims are met by the reference.

Applicant's Arguments

8. The Amendment filed on July 25, 2006 has been considered, however, is not fully persuasive. The applicant on page 4 of the response indicates that the written description and enablement rejections are traversed, stating that applicants have explicitly described all the GLP-1 compounds embodied by the claims and that the burden is on the examiner to establish a reasonable basis for questioning the enablement. Applicant further states that the claims are

Art Unit: 1656

limited to a GLP having a specific amino acid sequence and that GLP-1 is well known and characterized. This argument is not persuasive because the claims encompass a large genus of mutants of GLP-1. Claim 34 for example is directed to at least one modification from items a-c and within these items are laundry lists of substitutions that can be made. Thus the claims encompass all of a-c occurring to the claimed structure, which might no longer have its "GLP-1-like nature. The specific structure of the peptide encompassed in the formulation is not specifically or explicitly described as stated by applicant. To test all the possibilities for a shelf-stable formulation would require undue experimentation. Thus the rejection remains.

On page 6 of the response it is stated that the art of record should be withdrawn as the claim has been amended to delete "about" language. Note that the rejection remains. Applicant previously argued that the cited Hoffman reference does not disclose all the elements of the claims as the pH range exemplified by Hoffman is pH 8.1, whereas the claimed invention is directed to a pH range of 8.2-8.8. The reference clearly sets forth a pH range of 6.5 to 9.0 which falls within the recited ranges of 8.2-8.8 whether exemplified in the patent or not. This disclosure renders the claimed invention as anticipated. Thus, the rejection remains.

Conclusion

9. No claims are allowable.

Art Unit: 1656

10. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be reached at (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1656

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS *HR*

Patent Examiner *9/29/06*

Kath K
KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER